

STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 149968

TO: Kevin Weddington
Location: rem/3a65/3c70
Art Unit: 1614
Thursday, April 21, 2005

Case Serial Number: 10/665735

From: Edward Hart
Location: Biotech-Chem Library
REM-1A55
Phone: 571-272-2512

edward.hart@uspto.gov

Search Notes

Examiner Weddington,

Here are the results of the search you requested.

Please feel free to contact me if you have any questions.

Edward Hart

Requester's Full Name: K. Woodington Examiner #: 68082 Date: 4-5-05
 Art Unit: 1614 Phone Number: 272-0587 Serial Number: 10665,735
 Mail Box and Bldg/Room Location: 3A65 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. MEY

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

A composition comprising
 1) an opioid agonist
 2) naltrexone

The opioid agonist is selected from

hydromorphone
 oxycodone
 morphine
 hydrocodone
 hydromorphone.

STAFF USE ONLY

STAFF USE ONLY		Type of Search	Vendors and host where applicable
Searcher: _____	NA Sequence (#) _____	STN	_____
Searcher Phone #: _____	AA Sequence (#) _____	Dialog	_____
Searcher Location: _____	Structure (#) _____	Questel/Orbit	_____
Date Searcher Picked Up: _____	Bibliographic	Dr.Link	_____
Date Completed: _____	Litigation	Lexis/Nexis	_____
Searcher Prep & Review Time _____	Fulltext	Sequence Systems	_____
Clerical Prep Time: _____	Patent Family	WWW/Internet	_____
Online Time _____	Other	Other (specify)	_____

=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 13:44:27 ON 21 APR 2005

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 21 Apr 2005 VOL 142 ISS 17

FILE LAST UPDATED: 20 Apr 2005 (20050420/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his

(FILE 'HOME' ENTERED AT 13:30:11 ON 21 APR 2005)

FILE 'REGISTRY' ENTERED AT 13:30:24 ON 21 APR 2005
SET COST OFF

FILE 'REGISTRY' ENTERED AT 13:30:38 ON 21 APR 2005

E OPOID
L1 3 S E3
E AGONIST
L2 28 S E3

FILE 'HCAPLUS' ENTERED AT 13:31:11 ON 21 APR 2005

L3 3 S L1
L4 622 S L2
L6 625 L3 OR L4

FILE 'REGISTRY' ENTERED AT 13:31:52 ON 21 APR 2005

E NALTREXONE
L7 183 S E3

FILE 'HCAPLUS' ENTERED AT 13:32:08 ON 21 APR 2005

L8 2396 S L7
L9 2396 L7 AND L8
L11 3021 L6 OR L9
L12 9144 S OPIOID (L) AGONIST
E NALTREXONE/CT
L13 351463 S E3+ALL
L14 1127 S L12 AND L13

FILE 'REGISTRY' ENTERED AT 13:35:05 ON 21 APR 2005

E HYDROMORPHONE
L15 51 S E3

L16 E OXYCODONE
51 S E3
E MORPHINE
L17 1226 S E3
E HYDROCODONE
L18 17 S E3
E HYDROMORPHONE
L19 51 S E3

FILE 'HCAPLUS' ENTERED AT 13:36:10 ON 21 APR 2005

L20 1137 S L15
L21 1184 S L16
L22 42402 S L17
L23 973 S L18
L24 1137 S L19
L25 562 S L14 AND L20-24
L26 61 S L25 AND COMPOSITION
E PALERMO P/AU
L27 17 S E3,E5-E6
E COLUCCI R/AU
L28 31 S E3-E4,E8-E9
E KAIKO R/AU
L29 38 S E3-E7
L30 83 S L27-L29
L31 1 S L26 AND L30
L32 9 S L26 AND PREVENT?

FILE 'HCAPLUS' ENTERED AT 13:44:27 ON 21 APR 2005

=> d ibib abs hitrn l32 tot

L32 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:757712 HCAPLUS

DOCUMENT NUMBER: 139:271069

TITLE: Methods and **compositions** including nitric
oxide donors and opioid analgesics for pain relief

INVENTOR(S): Smith, Maree Therese; Brown, Lindsay; Harvey, Mark
Bradford Pullar; Williams, Craig Mckenzie

PATENT ASSIGNEE(S): The University of Queensland, Australia

SOURCE: PCT Int. Appl., 69 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

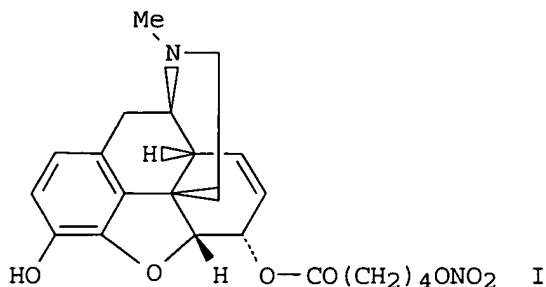
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003078437	A1	20030925	WO 2003-AU335	20030320
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

CA 2479098	AA	20030925	CA 2003-2479098	20030320
US 2003219494	A1	20031127	US 2003-393050	20030320
EP 1495026	A1	20050112	EP 2003-744274	20030320

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.:	US 2002-366594P	P 20020320
	WO 2003-AU335	W 20030320

OTHER SOURCE(S): MARPAT 139:271069
GI



AB **Compns.** and methods that induce, promote or otherwise facilitate pain relief are disclosed. These **compns.** and methods comprise a nitric oxide donor which either directly or indirectly **prevents**, attenuates or reverses the development of reduced opioid sensitivity, together with a compound which activates the opioid receptor that is the subject of the reduced opioid sensitivity. The **compns.** and methods **prevent** or alleviate pain, especially in neuropathic conditions and even more especially in peripheral neuropathic conditions such as

painful diabetic neuropathy. The preferred nitric oxide donor is L-arginine, while the preferred compds. which activate the opioid receptor are morphine and oxycodone. Conjugate compds. comprising the nitric oxide donor and an opioid analgesic are also disclosed. Preparation of morphine-NO donor conjugates, e.g. I, is also described.

IT 57-27-2, biological studies
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(nitric oxide donors and opioid analgesics for pain relief)

IT 52-26-6, Morphine hydrochloride 57-27-2D, derivs.
76-42-6, Oxycodone 76-42-6D, Oxycodone, derivs.
76-57-3 76-57-3D, derivs. 124-90-3, Oxycodone hydrochloride 466-99-9, Hydromorphone 466-99-9D, Hydromorphone, derivs. 41135-98-2 41135-98-2D, derivs.
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide donors and opioid analgesics for pain relief)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:737369 HCAPLUS

DOCUMENT NUMBER: 139:255368

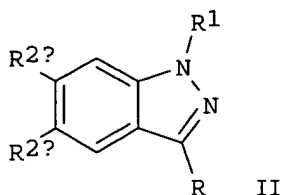
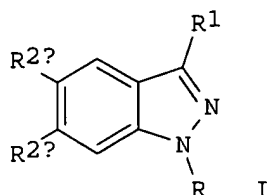
TITLE: Prokinetic agents for treating gastric hypomotility and related disorders

INVENTOR(S): Watson, John W.; Andrews, Paul L. R.; Woods, Anthony

J.
 PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 57 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003176421	A1	20030918	US 1999-476253	19991230
PRIORITY APPLN. INFO.:			US 1999-476253	19991230
OTHER SOURCE(S):	MARPAT 139:255368			

GI



AB Stasis is treated or **prevented** in all or any part or parts of the stomach of a patient, especially a human patient, in need of such treatment, where said stasis results from hypomotility in the stomach, particularly gastric hypomotility with delayed emptying of the liquid and/or solid contents of the stomach. Gastric or gastrointestinal disorders are also treated which are characterized by one or more symptoms selected from pain, nausea, vomiting, heartburn, postprandial discomfort, indigestion and gastroesophageal reflux. Such treatment or **prevention** is achieved by administering to the patient a therapeutically effective amount of an inhibitor of phosphodiesterase-4 (PDE4), including isoenzyme subtypes thereof, sufficient to treat or **prevent** such hypomotility or gastric or gastrointestinal disorder in said patient. The PDE4 inhibitor comprises I or II [preferably R = cyclopentyl or cyclohexyl; R1 = (C1-C2) alkyl; one of R2a and R2b = H and the other = Q; dashed line = single bond; m = 0, R113 and R114 are cis to each other; R113 = CN, R115 = H, R114 = carboxy, -CH2OH, -CH2C(=O)NH2].

Pharmaceutical **compns.** are also described which are useful for carrying out the above-mentioned methods of treatment and **prevention**, and which are also useful in the treatment of a gastric or gastrointestinal disorder in a patient which comprises with respect to said patient, (i) a sign or concomitant of diabetic neuropathy, anorexia nervosa, achlorhydria, gastrointestinal surgery, post-surgical recovery in the period of emergence from general anesthesia; or the administration of morphine and morphine-like opioids; (ii) a secondary aspect of a primary disease or disorder in said patient which is organic, wherein said disease or disorder involves particularly a gastroenteric or gastroesophageal organ or tissue, or an organ or tissue of the central nervous system of said patient; or (iii) an adverse side effect of a different therapeutic agent administered to said patient in the course of treating another unrelated disease or disorder in said patient.

IT 64-31-3, Morphine sulfate 71-68-1, Hydromorphone

hydrochloride 76-42-6, Oxycodone 76-57-3, Codeine
124-90-3, Oxycodone hydrochloride 25333-72-6, Oxycodone
terephthalate

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(as auxiliary therapeutic agent; prokinetic phosphodiesterase-4
inhibitor agents for treating gastric hypomotility and related
disorders)

IT 57-27-2, Morphine, biological studies
RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
unclassified); BIOL (Biological study)
(gastrointestinal disorder from; prokinetic phosphodiesterase-4
inhibitor agents for treating gastric hypomotility and related
disorders)

L32 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:590957 HCAPLUS

DOCUMENT NUMBER: 139:128042

TITLE: Methods and **compositions** for reducing the
development of drug tolerance and/or physical
dependence

INVENTOR(S): Whistler, Jennifer

PATENT ASSIGNEE(S): The Regents of the University of California, USA

SOURCE: PCT Int. Appl., 68 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003061594	A2	20030731	WO 2003-US2061	20030122
WO 2003061594	A3	20030925		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2476565	AA	20030731	CA 2003-2476565	20030122
US 2004024005	A1	20040205	US 2003-350270	20030122
EP 1476155	A2	20041117	EP 2003-715949	20030122
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
PRIORITY APPLN. INFO.:			US 2002-351442P	P 20020123
			US 2002-351466P	P 20020123
			WO 2003-US2061	W 20030122

AB The invention provides methods for reducing, **preventing** or
delaying the development of tolerance to certain drugs that target
G-protein coupled receptors (GPCR). The methods are generally carried out
by co-administering with the drug an **agonist** for the drug-target
GPCR that promotes the endocytosis of the targetted receptor. The methods
are particularly useful for drugs that target the **opioid**
receptors, for example morphine. The invention also provides

compns. comprising a drug and an **agonist** that are advantageous in **preventing** the development of tolerance to the drug that can develop when the drug is administered alone.

IT 57-27-2P, Morphine, biological studies 64-31-3P,
Morphine sulfate
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(methods and **compns.** for reducing development of drug tolerance and phys. dependence)

L32 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:133051 HCAPLUS

DOCUMENT NUMBER: 138:193266

TITLE: Oral dosage form comprising a therapeutic agent and an adverse-effect agent

INVENTOR(S): Wright, Curtis, IV; Carpanzo, Anthony E.

PATENT ASSIGNEE(S): Euro-Celtique, S.A., USA

SOURCE: PCT Int. Appl., 45 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013538	A1	20030220	WO 2002-US24889	20020805
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR			
US 2003044458	A1	20030306	US 2002-208817	20020801
EP 1414459	A1	20040506	EP 2002-761250	20020805
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			
DE 20220838	U1	20040624	DE 2002-20220838	20020805
BR 2002011781	A	20040727	BR 2002-11781	20020805
US 2005063909	A1	20050324	US 2004-948575	20040923
PRIORITY APPLN. INFO.:			US 2001-309791P	P 20010806
			US 2002-208817	A1 20020801
			WO 2002-US24889	W 20020805

AB The present invention provides an oral dosage form comprising a first **composition** and a second **composition**. The first **composition** comprises an effective amount of a therapeutic agent and the second **composition** comprises an effective amount of an adverse-effect agent. The adverse-effect agent is covered with a coating that is substantially insol. in the gastrointestinal tract. In one embodiment, the adverse-effect agent is coated with an outer base-soluble layer and an inner acid-soluble layer. The therapeutic agent can be uncoated or can be coated with a coating having an outer acid-soluble layer and an inner base-soluble layer. The dosage form discourages administration of the therapeutic agent by other than oral administration. Granules prepared from oxycodone

hydrochloride 20, spray-dried lactose 59.25, povidone 5, Eudragit RS 30D 10, and triacetin 2 mg, were spray coated with base-soluble coating solution containing Eudragit L, and then acid-soluble coating solution containing Eudragit El00.

Another granules prepared from naltrexone hydrochloride 5, spray-dried lactose 59.25, povidone 5, Eudragit RS 30D 10, and triacetin 2 mg, were spray coated with the acid-soluble coating solution, and then the base-soluble coating solution. The both granules were encapsulated in a gelatin capsule to make a dosage form of the present invention.

IT 57-27-2, Morphine, biological studies 62-67-9, Nalorphine 76-42-6, Oxycodone 76-57-3, Codeine 76-58-4, Ethylmorphine 124-90-3, Oxycodone hydrochloride 125-29-1, Hydrocodone 427-00-9, Desomorphine 466-97-7, Normorphine 466-99-9, Hydromorphine 467-18-5, Myrophine 509-60-4, Dihydromorphine 561-27-3, Diamorphine 639-48-5, Nicomorphine 14297-87-1, Benzylmorphine 16590-41-3, Naltrexone 20594-83-6, Nalbuphine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral dosage forms comprising therapeutic agents and adverse-effect agents having controlled-release coatings)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:666601 HCAPLUS

DOCUMENT NUMBER: 133:256811

TITLE: Pharmaceutical **compositions** containing dopamine agonists in combination with nitric oxide donors for treating and/or **preventing** sexual dysfunctions

INVENTOR(S): Garvey, David S.

PATENT ASSIGNEE(S): Nitromed, Inc., USA

SOURCE: PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054773	A1	20000921	WO 2000-US3709	20000310
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 1999-123920P P 19990312

OTHER SOURCE(S): MARPAT 133:256811

AB The present invention is directed to novel **compns.** comprising at least one dopamine agonist in combination with at least one nitric oxide donor (i.e. compds. that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide

synthase). The novel **comps.** may optionally comprise at least one therapeutic agent, such as, a vasoactive agent, an antiemetic agent, and mixts. thereof. The dopamine agonist is preferably apomorphine. The present invention is also directed to methods for treating and/or **preventing** sexual dysfunctions and/or enhancing sexual responses in patients. In other embodiments, the present invention is directed to methods treating or **preventing** neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinemia or myopia. The compds. and/or **comps.** of the present invention can also be provided in the form of a pharmaceutical kit (no data).

IT 58-00-4, Apomorphine. 314-19-2, Apomorphine hydrochloride 18426-20-5, N-n-Propyl norapomorphine
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmaceutical **comps.** containing dopamine agonists in combination with nitric oxide donors for treating and/or **preventing** sexual dysfunctions)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:425753 HCAPLUS

DOCUMENT NUMBER: 131:54010

TITLE: A method of **preventing** abuse of opioid dosage forms

INVENTOR(S): Palermo, Philip

PATENT ASSIGNEE(S): Euro-Celtique, S.A., Luxembourg

SOURCE: PCT Int. Appl., 47 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932120	A1	19990701	WO 1998-US27258	19981222
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2314896	AA	19990701	CA 1998-2314896	19981222
AU 9920899	A1	19990712	AU 1999-20899	19981222
AU 755790	B2	20021219		
BR 9813826	A	20001010	BR 1998-13826	19981222
EP 1041988	A1	20001011	EP 1998-965431	19981222
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
TR 200001828	T2	20001121	TR 2000-200001828	19981222
US 6228863	B1	20010508	US 1998-218663	19981222
JP 2001526229	T2	20011218	JP 2000-525111	19981222
NZ 505192	A	20030530	NZ 1998-505192	19981222

RU 2228180	C2	20040510	RU 2000-119779	19981222
NO 2000003278	A	20000822	NO 2000-3278	20000622
US 2002004509	A1	20020110	US 2001-815162	20010322
US 6627635	B2	20030930		
NZ 523964	A	20031031	NZ 2003-523964	20030131
PRIORITY APPLN. INFO.:			US 1997-68479P	P 19971222
			US 1998-218663	A1 19981222
			WO 1998-US27258	W 19981222
			NZ 2003-505192	A1 20030131

AB A method of reducing the abuse potential of an oral dosage form of an **opioid** analgesic is presented, wherein an analgesically effective amount of an orally active **opioid agonist** is combined with an **opioid** antagonist into an oral dosage form which would require a ≥ 2 -step extraction process to be separated from the **opioid agonist**. The amount of **opioid** antagonist is sufficient to counteract **opioid** effects if extracted together with the **opioid agonist** and administered parenterally. For example, a **composition** may contain hydrocodone bitartrate as **opioid agonist** and naltrexone-HCl as **opioid** antagonist; both drugs dissolve at pH <8, whereas .apprx.80% of hydrocodone and .apprx.10% of naltrexone are extractable at pH >10. Adding ingredients such as gelling agents or waxes to the **composition** makes separation of the **opioid agonist** and antagonist still more difficult. Addnl., the **opioid agonist** and antagonist may be combined in a ratio which is analgesically effective when administered orally to patients in pain, but is aversive in a phys. dependent subject.

IT **64-31-3**, Morphine sulfate **71-68-1**, Hydromorphone hydrochloride **124-90-3**, Oxycodone hydrochloride **143-71-5**, Hydrocodone bitartrate
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (method of **preventing** abuse of opioid dosage forms)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1996:350444 HCAPLUS

DOCUMENT NUMBER: 125:26295

TITLE: Method using bimodally acting **opioid agonist** and **opioid** antagonist for simultaneously enhancing analgesic potency and attenuating dependence liability caused by exogenous and endogenous **opioid agonists**
 INVENTOR(S): Crain, Stanley M.; Shen, Ke Fei
 PATENT ASSIGNEE(S): Albert Einstein College of Medicine, USA
 SOURCE: U.S., 18 pp., Cont.-in-part of U.S. Ser. No. 97,460.
 CODEN: USXXAM

DOCUMENT TYPE: Patent
 LANGUAGE: English

FAMILY ACC. NUM. COUNT: 13

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
US 5512578	A	19960430	US 1994-276966	19940719
US 5472943	A	19951205	US 1993-97460	19930727
US 5633259	A	19970527	US 1995-387679	19950213

US 5624932	A	19970429	US 1995-482713	19950607
CA 2195122	AA	19960201	CA 1995-2195122	19950718
WO 9602251	A1	19960201	WO 1995-US9974	19950718
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9532769	A1	19960216	AU 1995-32769	19950718
EP 808165	A1	19971126	EP 1995-929400	19950718
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 10507740	T2	19980728	JP 1995-505298	19950718
US 5580876	A	19961203	US 1995-552296	19951103
US 36547	E	20000201	US 1996-782452	19960113
US 5767125	A	19980616	US 1996-759590	19961203
US 6011004	A	20000104	US 1996-768221	19961217
US 6096756	A	20000801	US 1998-94977	19980616
US 2001006967	A1	20010705	US 1999-306164	19990506
AU 9941135	A1	19990923	AU 1999-41135	19990726
AU 9947399	A1	19991028	AU 1999-47399	19990906
US 6362194	B1	20020326	US 2000-585517	20000601
US 2002094947	A1	20020718	US 2002-37791	20020103
US 2003232744	A1	20031218	US 2002-319789	20021213

PRIORITY APPLN. INFO.:

US 1992-947690	B2	19920921
US 1993-97460	A2	19930727
US 1990-612847	B1	19901113
US 1992-977332	B2	19921117
US 1993-88503	B1	19930707
US 1993-153796	A1	19931117
US 1994-276966	A	19940719
US 1995-387679	A3	19950213
AU 1995-32769	A3	19950718
WO 1995-US9974	W	19950718
US 1995-552296	A1	19951103
US 1996-759590	A2	19961203
US 1998-94977	A2	19980616
US 2000-585517	A1	20000601
US 2002-37791	A1	20020103

AB A method is provided for selectively enhancing the analgesic potency of morphine and other clin. used bimodally-acting **opioid agonists** and simultaneously attenuating development of phys. dependence, tolerance, and other undesirable side effects caused by the chronic administration of said bimodally acting **opioid agonists**. The method comprises the co-administration of a bimodally acting **opioid agonist** which activates both inhibitory and excitatory **opioid** receptor-mediated functions of neurons in the nociceptive (pain) pathways of the nervous system and an **opioid** receptor antagonist which selectively inactivates excitatory **opioid** receptor-mediated side effects. Also provided is a method of using excitatory **opioid** receptor antagonists alone to block the undesirable excitatory side effects of endogenous bimodally acting **opioid agonists** which may be markedly elevated during chronic pain. Further provided are a method of long-term treatment of previously detoxified opiate, cocaine, and alc. addicts, using the excitatory **opioid** receptor antagonists, either alone or in combination with low-dose methadone, to **prevent** protracted phys. dependence, and **compns.** comprising an excitatory **opioid** receptor antagonist of the invention and a bimodally-acting **opioid agonist**. Chronic co-treatment of DRG neurons with morphine and ultra-low-dose naloxone or naltrexone **prevented** development of **opioid** excitatory supersensitivity ("dependence") and tolerance.

- IT 57-27-2, Morphine, biological studies 16590-41-3,
Naltrexone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bimodally acting **opioid agonist** and **opioid** antagonist for simultaneously enhancing analgesic potency and attenuating dependence liability and other side effects from exogenous and endogenous **opioid agonists**)
- IT 76-57-3, Codeine
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bimodally acting **opioid agonist** and **opioid** antagonist for simultaneously enhancing analgesic potency and attenuating dependence liability and other side effects from exogenous and endogenous **opioid agonists**)

L32 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1988:49242 HCAPLUS
DOCUMENT NUMBER: 108:49242
TITLE: Modulation of brain α 2-adrenoceptor and μ -opioid receptor densities during morphine dependence and spontaneous withdrawal in rats
AUTHOR(S): Ulibarri, Isabel; Garcia-Sevilla, Jesus A.; Ugedo, Luisa
CORPORATE SOURCE: Fac. Med., Univ. Pais Vasco, Leioa, E-48940, Spain
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1987), 336(5), 530-7
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English

- AB The densities of brain α 2-adrenoceptors and μ - **opioid** receptors, quantitated by means of the binding of the **agonists** [3H]clonidine and [3H]dihydromorphine, resp., were studied during the development of morphine dependence and spontaneous withdrawal in the rat. The oral administration of morphine (12-130 mg/kg for 3-21 days) led to inconsistent changes in α 2-adrenoceptor d. while the d. of μ - **opioid** receptors was down-regulated. In contrast, spontaneous opiate withdrawal (3-72 h) increased the d. of α 2-adrenoceptors while the d. of μ - **opioid** receptors was rapidly up-regulated to control values. In the hypothalamus, but not in other brain regions, the increase in α 2-adrenoceptor d. after withdrawal followed a time course (3-72 h) related to the severity of the abstinence syndrome. Thus, there was a pos. and significant correlation between the severity of withdrawal and the d. of α 2-adrenoceptors in the hypothalamus. Short-term treatment with clonidine, **prevented** the morphine withdrawal-induced increases in α 2-adrenoceptor d. in various brain regions, but not in the hypothalamus. Apparently, modulation of hypothalamus α 2-adrenoceptor d. during morphine withdrawal is a relevant physiol. mechanism by which the opiate abstinence syndrome is counteracted.
- IT 57-27-2, Morphine, biological studies
RL: BIOL (Biological study)
(dependence on, brain α 2-adrenergic and μ -opioid receptors in)

L32 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1982:608322 HCAPLUS
DOCUMENT NUMBER: 97:208322
TITLE: Calmodulin increases in selective brain regions with opioid dependence

AUTHOR(S): Bonnet, K. A.; Engelberg, L.; Gusik, S. A.
CORPORATE SOURCE: Sch. Med., New York Univ., New York, NY, 10016, USA
SOURCE: Life Sciences (1982), 31(20-21), 2295-8
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acute challenge of thalamic membranes with **opioid agonists** displaced Ca and **prevent** isoproterenol [7683-59-2] stimulation of adenylate cyclase [9012-42-4]. Chronic morphine [57-27-2] administration for 3 days or 3 wk increased the level of calmodulin in membranes of thalamus, but not in periaqueductal gray, striatum, amygdala, or hypothalamus. Thus, calmodulin may play an important role in the biol. basis of phys. dependence on **opioids**.
IT 57-27-2, biological studies
RL: BIOL (Biological study)
(dependence on, calmodulin of brain thalamus in)